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The relation between hyponatremia at presentation, severity of disease and length of stay in patients with bronchiolitis

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Abstract

Aim: In this study, we aimed to investigate the relationship between hyponatremia at presentation and severity of disease and length of stay in children admitted to hospital with acute bronchiolitis.

Material and Methods: This cross-sectional study was performed at a tertiary care hospital between May 2017 and April 2018. One hundred seventy children aged 1-24 months admitted with a diagnosis of acute bronchiolitis were included in the study. Demographic and biochemical data were recorded together with data associated with clinical course and length of stay.

Results: Hyponatremia was present in 62 (36.4%) of the 170 patients. Thirteen patients (20.9%) in the hyponatremic group were diagnosed with moderate bronchiolitis and 17 (27.5%) with severe bronchiolitis, while in the normonatremic group, 14 (12.9%) with moderate bronchiolitis and 9 (8.4%) with severe bronchiolitis (p<0.001). High-flow nasal cannula (FNC) requirement was present in 17 patients in the hyponatremic group and 17 in the normonatremic group (p=0.001). The risk of development of severe bronchiolitis increased 0.085-fold in patients with hyponatremia. The median length of hospitalization was 5 (2-21) days in the hyponatremic group and 4 (2-11) days in the normonatremic group (p=0.001). Hyponatremia increased length of stay approximately 4.7-fold.

Discussion: The risk of developing severe bronchiolitis and non-invasive mechanical ventilation requirements was significantly higher in the hyponatremic group. The length of hospital stay was greater in cases of bronchiolitis with hyponatremia. We think that measuring sodium levels during hospitalization in cases of bronchiolitis will be useful in predicting the risk of development of severe bronchiolitis and extended length of stay.

Keywords

Bronchiolitis; Hyponatremia; Infant; Length of stay

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Introduction

Acute bronchiolitis is one of the respiratory tract diseases frequently encountered in infancy. It is particularly common in children under 6 months and is the most frequent cause of hospitalization in children under 2 years [1, 2].

There is a few studies investigated the relationship between hyponatremia and length of hospital stay or poor outcomes in cases of bronchiolitis. The reported prevalence of hyponatremia in cases of severe bronchiolitis admitted to intensive care units is between 16% and 33% [3,4]. One study of cases of moderate-severe bronchiolitis aged less than 6 months presenting to the emergency department measured sodium levels using direct potentiometry and determined a prevalence of hyponatremia of 57% [5]. It has been proposed that hyponatremia may develop as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypotonic fluid use, or iatrogenic fluid loading [6]. Hyponatremia may be life-threatening since the passage of fluid into brain cells and alveoli is increased. It has also been suggested that in addition to the direct neurotoxic effects of viruses and upper respiratory tract obstruction, hyponatremia may also be responsible for neurological complications such as apnea, seizure and lethargy, seen in 1.2% of bronchiolitic patients admitted to the pediatric ward and in 39% of patients in the pediatric intensive care unit [7,8]. The mortality rate in bronchiolitis is generally less than 1%, although it may increase dramatically, to as high as 13%, in the presence of hyponatremia [4].

The purpose of this study was to investigate the relationship between severity of disease and length of hospitalization and hyponatremia at the time of presentation in children aged 1-24 months hospitalized with a diagnosis of bronchiolitis.

Material and Methods

This prospective cross-sectional study was performed at the Adıyaman University School of Medicine, Department of Pediatrics. The study was designed in accordance with the principles of the Helsinki Declaration, and was approved by the Adıyaman University Medical Faculty Clinical Research Ethical Committee (No. 2017/5-3, dated 20.06.2017). Informed consent forms were received from individuals responsible for the care of the patients enrolled.

Study population

One hundred seventy children aged 1-24 months hospitalized with a diagnosis of acute bronchiolitis between May 2017 and April 2018 were included in the study. Patients with accompanying pathologies such as gastroenteritis, pneumonia, bacteremia, meningitis, pyelonephritis, hypertriglyceridemia or hyperglycemia, with histories of chronic diseases, with a history of recent surgery, diuretic use or conditions capable of altering serum sodium levels, such as previously undiagnosed SIADH, and patients started on parenteral fluid support before being taken for tests were excluded.

Acute bronchiolitis has been defined as tachypnea, subcostal-intercostal retraction, prolonged expirium, and wheezing or rales/rhonchi at the physical examination in addition to respiratory system symptoms such as nasal discharge, cough, wheezing and respiration difficulty, together with a flattened diaphragm and hyperinflation at chest x-ray [9, 10]. Depending on clinical status, cases were divided into three groups, mild bronchiolitis (cases with mild retraction, a respiratory rate of 41-55 breaths per minute for <6 months, 31-45 for >6 months, and arterial saturation [SaO2] of 92-94% at room temperature), moderate bronchiolitis (cases with moderate retraction, a respiratory rate of 56-70 breaths per minute for <6 months, 46-60 for >6 months, and SaO2 90-91%), and severe bronchiolitis (cases with severe retractions, a respiratory rate of ≥71 for <6 months, ≥61 for >6 months, and SaO2 ≤89%) [11].

Hyponatremia was defined as a serum sodium concentration below 135 mEq/L. Hyponatremic cases were divided into three groups based on serum sodium value: mild (cases with serum sodium levels of 130-134 mEq/L), moderate (serum sodium levels of 125-129 mEq/L), and severe (serum sodium levels ≤124 mEq/L) [12].

Serum osmolality was calculated using the formula 2 x Na+2 + (Glucose/18) + (Urea/2.8). Cases meeting all diagnostic criteria of serum sodium ≤135 mEq/L, serum osmolality < 280 mOsm/kg, sodium in spot urine > 30 mEq/L, urine osmolality > 100 mOsm/kg, absence of hypovolemia and dehydration, normal thyroid and adrenal functions, and absence of advanced liver, kidney, and heart disease were regarded as SIADH [13].

Data acquisition

Blood specimens collected from all cases within 2 hours of admission before any fluid therapy were studied in the laboratory, and serum sodium levels were subsequently investigated once every 72 hour during hospitalization. Demographic data including age, sex, type of birth, birth week, history of neonatal intubation, type of nutrition, duration of symptoms, atopy, additional disease, family history of atopy, characteristics of the place of residence (rural or urban, presence of animals in the home, and dampness in the home), maternal smoking status during pregnancy, and smoking status within the home were recorded for patients admitted with a diagnosis of bronchiolitis. Data regarding clinical course were also recorded, including respiratory rate, heart rate, oxygen requirement, the severity of bronchiolitis, high-flow nasal cannulation (HFNC) requirement, intubation requirement, length of hospitalization, and fluid used. Laboratory results such as albumin, glucose, urea, creatinine, sodium, potassium, chloride, alanine aminotransferase (ALT), serum osmolality, and blood gas values (pH, carbon dioxide [pCO2] and bicarbonate [HCO3]), sodium in spot urine, and urine osmolality were also recorded.

Laboratory analysis

Venous blood specimens were collected from all patients during hospitalization. Biochemical parameters and sodium levels in spot urine were investigated with an Architect c8000 Processing Module (Abbott Laboratories, Japan) device. Blood gas was investigated using an ABL 700 Series (Radiometer Medical ApS, Denmark) device, and urine osmolality with a Beckman Coulter AU5811 (Diamond Diagnostics Inc., USA) device.

Statistical Analysis

Data were analyzed on SPSS (Statistical Package for Social Sciences Statistical Software) version 23.0 (SPSS, Inc., Chicago, USA) software. The chi-square test was employed in the analysis of categorical data. The Kolmogorov-Smirnov test was applied to determine whether continuous data were compatible with a normal distribution. Normally distributed data were expressed

as mean ±standard deviation and were analyzed using the Independent Two Samples t-test. Non-normally distributed data were expressed as mean values (minimum-maximum) and were analyzed using the Mann-Whitney U test. P values <0.05 were regarded as statistically significant.

Linear multiple regression analysis (Backward LR model) was applied in order to identify independent predictor markers affecting length of hospitalization. Ordinal regression analysis was employed to determine independent markers capable of use in predicting the degree of severity of bronchiolitis.

Results

Sixty-two (36.4%) patients were hyponatremic and 108 (63.6%) were normonatremic. Mild hyponatremia was determined in 53 patients (85.4%) and moderate hyponatremia in nine (14.6%), while severe hyponatremia was not observed in any case. Boys represented 67.8% of hyponatremic cases and girls 32.2%.

No statistically significant difference was determined between the groups in terms of sex, age, duration of symptoms before presentation, type of birth, neonatal intubation, type of nutrition, recurrent wheezing, atopy, familial atopy, place of residence, presence of animals in the home, presence of damp in the home, smoking in the home, or maternal history of smoking during pregnancy (p>0.05).

Thirty-two (51.6%) patients in the hyponatremic group were diagnosed with mild, 13 (20.9%) with moderate, and 17 (27.5%) with severe bronchiolitis. In the normonatremic group, 85 (78.7%) patients were diagnosed with mild, 14 (12.9%) with moderate, and nine (8.4%) with severe bronchiolitis. The prevalence of moderate and severe bronchiolitis was significantly higher in the hyponatremic group than in the normonatremic group (p<0.001). Oxygen requirements were present in 31 (50%) of the hyponatremic group and 23 (21.2%) of the normonatremic group (p<0.001). Seventeen (27.4%) patients in the hyponatremic group and nine (0.08%) in the normonatremic group required HFNC (p=0.001). One patient in each group was intubated. No statistically significant difference was determined between the two groups in terms of intubation requirement (p=0.589). Median (minimum-maximum) length of hospitalization was 5 (2-21) days in the hyponatremic group and 4 (2-11) days in the normonatremic group (p=0.001). The length of hospitalization was significantly longer in the hyponatremic group (Table 1).

Table 1. Comparison of clinical data of hyponatremic and normonatremic groups

	Hyponatremic group (n=62)	Normonatremic group (n=108)	P
Oxygen requirement	31[a]	23	<0.001*
High-flow nasal cannula (HFNC) requirement	17[a]	9	0.001*
Intubation requirement	1[a]	1	0.589
Bronchiolitis severity			
Mild	32[a]	85	<0.001*
Moderate	13	14	
Severe	17	9	
Length of stay (day)	5(2-21)[b]	4(2-11)	0.001*

[a] Count, Chi-square test; [b] median (minimum-maximum), Man-Whitney U test; *p<0.05

Table 2. Ordinal Regression Analysis of independent markers to be used in predicting severity of bronchiolitis

	Beta	Wald	Odds Ratio	P
[Sex=Male]	0.966	3.552	2.627 (-0.039 – 1.971)	0.059
[Sex=Female]	0[a]	.		.
[Age=15 months]	-4.070	5.813	0.017 (-7.378 – -0.761)	0.016*
[Age=23 months]	0[a]	.		.
[Type of birth=caesarean delivery]	-0.536	1.205	0.585 (-1.492 – 0.421)	0.272
[Type of birth=vaginal birth]	0[a]	.		.
[Birth week=preterm]	0.428	0.321	1.534 (-1.052 – 1.908)	0.571
[Birth week=term]	0[a]	.		.
[History of neonatal intubation=no]	0.168	0.029	1.183 (-1.779 – 2.115)	0.866
[History of neonatal intubation=yes]	0[a]	.		.
[Type of nutrition=only breast milk]	-0.524	0.289	1.689 (-2.435 – 1.387)	0.591
[Type of nutrition=only formula milk]	2.288	4.199	9.855 (0.100 – 4.477)	0.040*
[Type of nutrition=only additional food]	-0.615	0.217	0.540 (-3.207 – 1.976)	0.642
[Type of nutrition=breast milk+formula milk]	0.565	0.462	1.759 (-1.064 – 2.195)	0.497
[Type of nutrition=breast milk+ additional food]	0[a]	.		.
[History of recurrent bronchiolitis=no]	-0.439	0.538	0.645 (-1.614 – 0.735)	0.463
[History of recurrent bronchiolitis=yes]	0[a]	.		.
[History of Atopy=no]	-3.291	17.865	0.037 (-4.817 – -1.765)	<0.001*
[History of Atopy=yes]	0[a]	.		.
[Family history of atopy=no]	0.308	0.122	1.361 (-1.419 – 2.035)	0.726
[Family history of atopy=yes]	0[a]	.		.
[Place of residence=rural]	-0.696	1.616	0.498 (-1.769 – 0.377)	0.204
[Place of residence=urban]	0[a]	.		.
[Presence of dampness in the home=no]	-0.633	1.148	0.531 (-1.791 – 0.525)	0.284
[Presence of dampness in the home=yes]	0[a]	.		.
[Presence of animals in the home=no]	1.297	1.417	3.658 (-0.839 – 3.432)	0.234
[Presence of animals in the home=yes]	0[a]	.		.
[Maternal smoking during pregnancy =no]	-0.325	0.101	0.723 (-2.335 – 1.685)	0.751
[Maternal smoking during pregnancy=yes]	0[a]	.		.
[Smoking in the home=no]	-0.918	2.704	0.399 (-2.013 – 0.176)	0.100
[Smoking in the home =yes]	0[a]	.		.
[Hyponatremia=no]	-2.463	22.026	0.085 (-3.492 – 1.434)	<0.001*
[Hyponatremia=yes]	0[a]	.		.

CI, Confidence Interval; *p<0.05

Table 3. Linear Multiple Regression Analysis (Backward Model) of independent markers to be used in predicting length of stay

	Beta	Odds Ratio (95% Confidence Interval)	P
Sex	-0.170	0.377 (-1.796 – -0.155)	0.020*
History of Atopy	0.185	4.697 (0.354 – 2.739)	0.011*
Hyponatremia	0.271	4.688 (0.730 – 2.361)	<0.001*

*p<0.05

Mean serum osmolarity was 273.6±3.8 mOsm/L in the hyponatremic group and 284.5±4.3 mOsm/L in the normonatremic group (p<0.001). SIADH was determined in 33 patients in the hyponatremic group. No hyponatremia developed in any case that was normonatremic at baseline. No clinical findings of hyponatremia (nausea, vomiting, headache, lack of appetite, fatigue, lethargy, apathy, agitation, muscle cramps, and convulsion) were observed in any of our hyponatremic patients with bronchiolitis.

Ordinal logistic regression analysis was applied in order to identify independent predictors of the severity of bronchiolitis. The probability of developing severe bronchiolitis was 9.855 times higher in children who had never breastfed compared to those receiving mother's milk + formula milk + additional food (p=0.040), 0.037 times higher in subject with atopy than in those without (p<0.001), and 0.085 times higher in subjects with hyponatremia than in those without (p<0.001) (Table 2).

Linear multiple regression (backward LR model) was applied in order to identify independent predictors of length of hospitalization in bronchiolitic cases. Female gender was observed to reduce length of hospitalization 0.4-fold (p=0.020), while a history of atopy increased the length of hospitalization approximately 4.7-fold (p=0.011) and hyponatremia also increased it approximately 4.7-fold (p<0.001) (Table 3).

Discussion

Acute bronchiolitis is responsible for 3-5% of emergency department presentations in infancy. No effectiveness has been proved for therapeutic methods other than hydration, nutrition, and oxygenation [10]. A gradual decrease in hospital presentations due to bronchiolitis has been reported, although numbers of cases requiring invasive or non-invasive mechanical ventilation have increased, and this has led to greater complication rates and costs [1]. It is therefore important to identify factors necessitating hospitalization in cases of bronchiolitis and that thus prolongs hospital stay or leads to the development of complications.

Hyponatremia has been reported to be capable of occurring in respiratory tract infections in addition to pathologies such as meningitis, encephalitis, head trauma, use of some drugs, and long-term hypotonic fluid use in hospitalized patients [14-16]. Hyponatremia has particularly been reported in association with SIADH in cases of pneumonia among respiratory tract problems [12]. Recent studies have investigated the relation between moderate-severe bronchiolitis and hyponatremia, and the development of neurological complications such as apnea and hyponatremia [3-6, 8]. This study examined the relation between hyponatremia and degree of bronchiolitis and length of hospitalization in cases of mild, moderate, and severe bronchiolitis.

Milani et al. [5] observed hyponatremia in 91 cases of moderate-severe bronchiolitis, with hyponatremia being mild in 74 cases (81.3%), moderate in 15 (16.4%), and severe in one (1.3%). Hyponatremia was present in 62 cases (36.4%) in our study, mild in 53 (85.4%) and moderate in nine (14.6%). No severe hyponatremia was determined in any of our patients.

Luu et al. [3] reported a mean age of 11.2 months in their hyponatremic group, but no significant difference in terms of age compared to the normonatremic group. Hasegawa et al. [4] reported that hyponatremia developed more frequently in patients with bronchiolitis aged 12-24 months. The mean age of the hyponatremic group in our study was 9.2 months, and we determined no statistically significant difference in terms of age compared with the normonatremic group.

Hasegawa et al. [4] compared the two groups in terms of the history of breastfeeding and reported that 19 patients (50%) in the hyponatremic group and 105 (54.4%) in the normonatremic group received mother's milk, and that the difference between the groups was not statistically significant. In our study, 50 patients (80.6%) in the hyponatremic group and 90 (83.3%) in the normonatremic group had a history of breastfeeding. Our rate of breastfeeding was higher in both groups compared with those of other studies. However, the risk of development of severe bronchiolitis was 9.8-fold higher in patients who were not breastfed compared to those who received mother's milk and mixed nutrition.

Shibli et al. [8] determined that neurological complication developed in one case of severe hyponatremia with a serum sodium level of 123 mmol/L among 84 cases of bronchiolitis with hyponatremia detected at presentation. They reported using hypotonic fluid containing 0.18% NaCl in that case. Shein et al. [6] also reported that the use of hypotonic fluid in patients with bronchiolitis led to hyponatremia, and that this resulted in poor outcomes. In our study, no neurological complications were observed in any case. We attribute this to the absence of any cases of severe hyponatremia (<125 mmol/L) in our study and to hypotonic fluid not being used during hospitalization.

Although several studies have investigated the relationship between the prevalence of SIADH and pneumonia, very few have examined the association between the prevalence of SIADH and acute bronchiolitis. One study from japan determined SIADH in 38.7% of cases of pneumonia, in 22.9% of cases of bronchitis and bronchiolitis, and in 13.3% of cases of pharyngitis and laryngitis [17]. Hasegawa et al. [18] reported hyponatremia in 73 out of 1191 patients admitted to the pediatric department, and that 10 of these were cases diagnosed with bronchiolitis. SIADH was determined in 33 (19.4%) of the bronchiolitis cases included in our study. However, considering that hyponatremia was not determined in 62 patients, we think that pathologies other than SIADH may be involved in the etiology of hyponatremia.

Anıl et al. [19] suggested that the presence of hyponatremia does not exacerbate the disease in cases of lower respiratory tract infection. However, it is difficult to standardize these data since that study evaluated not cases of bronchiolitis alone, but all diseases such as bronchiolitis, pneumonia, and bronchopneumonia under the heading of lower respiratory tract infections. Milani et al. [5] also reported no relation between hyponatremia and degree of severity of bronchiolitis. Hasegawa et al. [4] examined cases of moderate-severe bronchiolitis and reported a relation between hyponatremia and severity of bronchiolitis, greater mechanical ventilation requirements in hyponatremic cases, and that hyponatremia exacerbated the disease. Luu et al. [3] also reported no difference in terms of intubation requirements between hyponatremic and normonatremic cases, but that non-invasive

ventilation requirements were higher in hyponatremic cases. While we observed no difference between our hyponatremic and normonatremic groups in terms of mechanical ventilation requirements, the frequency of development of severe bronchiolitis, and non-invasive ventilation requirements, such as HFNC, were significantly higher in the hyponatremic cases. In addition, ordinal regression analysis revealed a correlation between the development of severe bronchiolitis and hyponatremia, with hyponatremia increasing the risk of severe bronchiolitis 0.085-fold.

Don et al. [20] reported lengths of hospitalization of 5.35 days in hyponatremic cases and 5.50 days in non-hyponatremic cases in a patient group diagnosed with atypical pneumonia, and that hyponatremia did not affect the length of hospital stay in patients with pneumonia. In their study of children with pharyngitis, laryngitis, bronchiolitis, and pneumonia, Kaneko et al. [17] also reported that hyponatremia did not affect the length of hospitalization. However, Luu et al. [3], Hasegawa et al. [4] and Shein et al. [6] investigated the relationship between hyponatremia and severity of bronchiolitis and determined longer hospital stays in cases with hyponatremia compared to those without. We also determined longer hospitalization in bronchiolitis cases with hyponatremia compared to the normonatremic group. In addition to hyponatremia, male gender and history of atopy also prolonged length of hospital stay.

The limitations of our study may be listed as the relatively low patient number and the low number of patients with severe bronchiolitis.

In conclusion, the risk of development of severe bronchiolitis and of oxygen and non-invasive ventilation requirements was higher in the hyponatremic group compared to the normonatremic group. Hyponatremia was found to prolong hospitalization in cases of bronchiolitis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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